REMARKS

Restriction/Election

1. In the April 21, 2008 Office Action, the Examiner imposed a restriction requirement under 35 U.S.C. §121 against claims 1-15 and 17-27, and required that an election be made between:

Group I: claim(s) 1-9, 18-21, and 25-26, drawn to peptides;

Group II: claim(s) 10-15, drawn to nucleic acids, host cells, and methods of making peptides;

Group III: claim(s) 17 and 27, drawn to methods of producing delivery systems; and

Group IV: claim(s) 22-24, drawn to methods of modulating expression.

Applicants hereby elect Group I, claim(s) 1-9, 18-21 and 25-26, drawn to peptides.

2. The Examiner has further required a sequence election applicable to all groups. According to the Examiner, each sequence is patentably distinct because they are structurally unrelated sequences. Specifically, the Examiner states:

> "If SEQ ID NO: 17 is elected, then SEQ ID NOS: 29-36 would be examined with SEQ ID NO: 17. These sequences are disclosed as being truncated forms of SEQ ID NO: 17. Applicant is advised that examination will be restricted to only the elected SEQ ID NO and should not be construed as a species election."

Applicants wish to elect SEQ ID NO: 17 *with traverse*.

Applicants note that the Examiner states that SEQ ID NOS: 29-36 would be examined with SEQ ID NO: 17. Applicants argue that SEQ ID NOS: 24-36 (instead of SEQ ID NOS: 29-36) should be examined because the peptides of SEQ ID NOS: 24-28 are also truncated forms of SEQ ID NO: 17. Furthermore, Applicants argue that SEQ ID NOS: 1-6, 9-14 and 16-22, as well as the truncated forms of SEQ ID NO:17, namely SEQ ID NOS: 24-36, should also be examined for the reasons stated below.

All of the peptides not only share a common functional feature, namely, their capacity of binding to TGF-β1, but, contrary to the opinion of the Examiner, said peptides share additional common structural features which make them structurally related peptides. As shown in Annex 1, using conventional amino acid sequence alignment studies (taking the most active peptide [SEQ ID NO: 17] (p17)] as the reference peptide], it can be seen that:

- all the peptides have, at least, a basic amino acid (R, K, H) at positions X1 and X2 of their amino acid sequence;

- all the peptides have at least one hydrophobic amino acid at positions X3, X4 and X5 of their amino acid sequence; in some cases, two of the three positions are occupied by hydrophobic amino acids which are further aromatic amino acids (W, F or Y);

- all the peptides have at least one basic (R, K, H) or a hydrophilic amino acid (P, S) at positions X7, X8 and X9 of their amino acid sequence;

- the net electric charge of all the peptides, at physiological pH (7.2), ranges between +2 and +5; and

- the isoelectric point (pI) of all of the peptides ranges between 11 and 12.5.

Therefore, based on the following, all of these features suggest that all of the peptides represented in SEQ ID NOS: 1-6, 9-14 and 16-22 share in common a region of interaction with TGF-β1 which is important for its activity. Indeed, this interaction appears to affect, either directly or indirectly, to the region involved in the interaction with TGF-β1 receptor(s).

Furthermore, *in silico* experiments carried out by the inventors indicate that there is a common amino acid sequence (activity nucleus) in all of these peptides responsible for the recognition and binding of TGF-β1. As shown in Annex 2, SEQ ID NO: 17 has a 5 amino acid region which interacts with TGF-β1. The 5 amino acid region (KRIWF) is included within the common amino acid sequence (activity nucleus) deducted by the amino acid sequence alignment studies (see, *e.g.*, Annex 1). Therefore, based on the related structure, all of the peptides share a functional feature, namely, the capacity of binding directly to, or close to, the region of TGF-β1 which is involved in the interaction with TGF-β1 receptor(s), a very important region for the activity of TGF-β1.

Therefore, based on the above arguments, Applicants respectfully request that SEQ ID NOS: 1-6, 9-14, 16-22 and 24-36 be considered for examination.

Petition for Extension of Time/Fees Payable

Applicants hereby petition for a one (1) month extension of time, extending the deadline for responding to the April 21, 2008 Restriction Requirement from May 21, 2008 to June 23, 2008. As such, the fee of $120.00 specified in 37 C.F.R. §1.17(a)(1) for such one (1) month extension is due.

The total fee of $120.00 is being paid by check. Authorization is also hereby given to charge any deficiency in applicable fees, or credit any overcharges, for this response to Deposit Account No. 13-4365 of Moore & Van Allen, PLLC.

Conclusion

Based on the foregoing, claims 1-9, 18-21, and 25-26 are in form and condition for examination.

If any additional issues remain, the Examiner is requested to contact the undersigned attorney at (919) 286-8000 to discuss same.

Respectfully submitted,

MOORE & VAN ALLEN PLLC

Date: June 23, 2008

By: _____

Eric F. Wagner
Registration No. 53,730
Moore & Van Allen PLLC
430 Davis Drive, Suite 500
Morrisville, NC 27560-6832
Telephone: (919) 286-8000
Facsimile: (919) 286-8199

Annex 1

Relative position of the amino acids with respect to the consensus sequence

	R1															R2			KRHS	WYF	pI	charge pH7,2	HF H&W	Biological activity %inhibition *in vivo*
Péptido	-4	-3	-2	-1	x1	x 2	x3	x4	x5	x6	x7	x8	x9	x10	x11	x12	13	14	15						
p17	-	-	-	-	K	R	I	W	F	i	P	R	S	s	w	Y	e	r	a	6/4		11	+3	-0,1	100
p6	-	p	p	y	H	R	F	W	r	g	H	R	H	a	v	q	-	-	-	6/3		11,5	+3	-2,5	89
p11	-	-	-	-	w	H	k	Y	F	l	R	R	P	l	s	V	r	t	r	7/3		12	+5	1,1	35
p4	-	-	-	-	R	l	A	h	s	h	R	H	R	s	h	V	a	l	t	9/0		12,3	+3	1,1	56
p13	-	-	-	-	R	K	W	F	L	q	H	R	R	m	p	V	s	v	l	6/2		12,3	+4	-1,8	27
p14	-	-	s	g	R	R	h	L	h	r	H	H	i	f	s	L	p	-	-	9/1		12,3	+3	-0,3	50
p2	-	-	-	d	R	R	I	F	W	w	S	n	R	s	a	p	g	a	-	5/3		11,75	+3	0,7	39
p3	-	r	f	f	T	R	F	p	W	h	y	H	a	s	r	L	-	-	-	6/5		11,75	+3	-7,6	2
p18	m	p	l	s	R	y	W	W	L	f	S	H	R	p	r	-	-	-	-	6/4		11,75	+3	-7,4	0
p9	-	-	-	g	w	H	s	L	L	h	S	R	y	h	r	I	a	a	-	7/2		11	+2	-7	21
p1	-	-	-	d	R	R	I	F	W	w	S	l	R	s	a	p	g	a	-	5/3		11,75	+2	-1,3	12
p15	-	-	-	-	g	w	I	t	F	h	R	R	H	h	d	r	v	l	s	7/2		11,75	+2	-0,6	16
p19	-	-	-	-	R	H	L	s	h	f	K	w	l	r	s	h	g	l	d	8/2		11	+2	-0,2	21
p12	-	-	-	-	w	H	k	Y	F	l	R	R	P	l	s	V	g	l	g	5/3		11	+3	-6,3	0
p8	-	w	h	w	R	H	r	I	p	l	q	l	a	a	g	r	-	-	-	5/2		12,3	+3	-5	0
p5	-	-	-	-	R	R	W	v	r	y	P	v	H	l	h	s	p	i	v	6/2		11,75	+3	-5,5	0
p20	-	-	-	-	R	R	F	h	F	h	S	R	m	v	a	V	d	n	s	7/2		11,75	+2	2	0
p21	-	-	h	v	R	l	h	h	Y	l	R	H	R	s	l	p	n	-	-	8/1		11,75	+3	-1,7	0
p16	-	-	-	-	R	l	h	g	h	r	S	H	R	f	t	h	v	a	q	8/1		12,3	+3	0,8	0
p22	-	-	-	-	v	p	M	a	L	n	H	g	v	y	v	m	v	s	s	3/1		7,25	0	-12,9	0
p10	-	f	v	w	v	R	F	h	r	l	P	R	q	i	y	t	-	-	-	4/4		11,75	+3	-9	0
p7	-	-	-	-	H	R	I	s	h	f	a	H	R	y	l	a	r	l	h	8/2		11,75	+3	-3,9	0

Basic residues — Hydrophobic residues (aromatic) — Basic o hydrophilic residues

in vivo active peptides — *in vivo* inactive peptides

Figure 1. Sequence alignment of the peptides disclosed by US 10/569,012 [p1-17 correspond to the peptides identified as SEQ ID NOs: 1-17, respectively]. This figure includes the net charge at physiological pH of each peptide, their isoelectric point, their hydrophilicity (according to the Hopp & Woods scale), the ratio between basic or hydrophilic residues (K,R,H,S) and aromatic residues (W,Y,F) and their *in vivo* activity. This activity is measured on the basis of the amount of collagen type I mRNA induced in mice after oral administration of carbon tetrachloride. The amino acids which, with respect to the consensus sequence, appear to be very conserved are typed in red whereas the semiconserved amino acids are typed in blue.

Annex 2

Computer prediction (model) of the molecular interaction between peptide p17 and TGF-β1

Figure A2.1 shows a possible orientation of a region of p17 in the main hydrophobic cavity of the molecular surface of TGF-β1. Figure A2.2 shows the orientation and interaction of the amino acids of the fragment of p17 with respect to the molecular surface of TGF-β1 in the model considered.

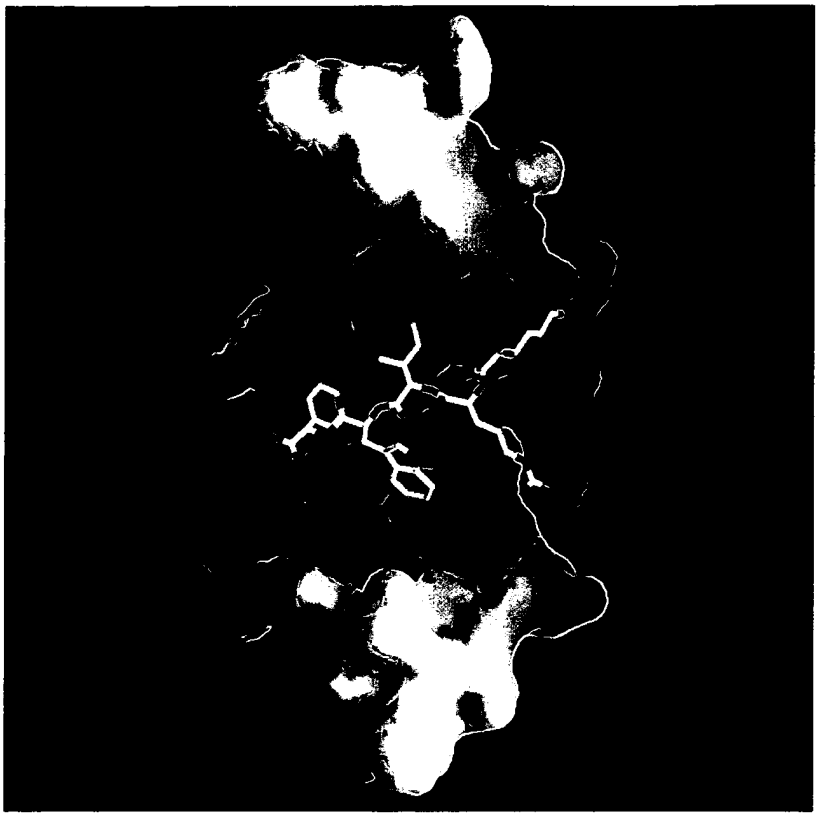
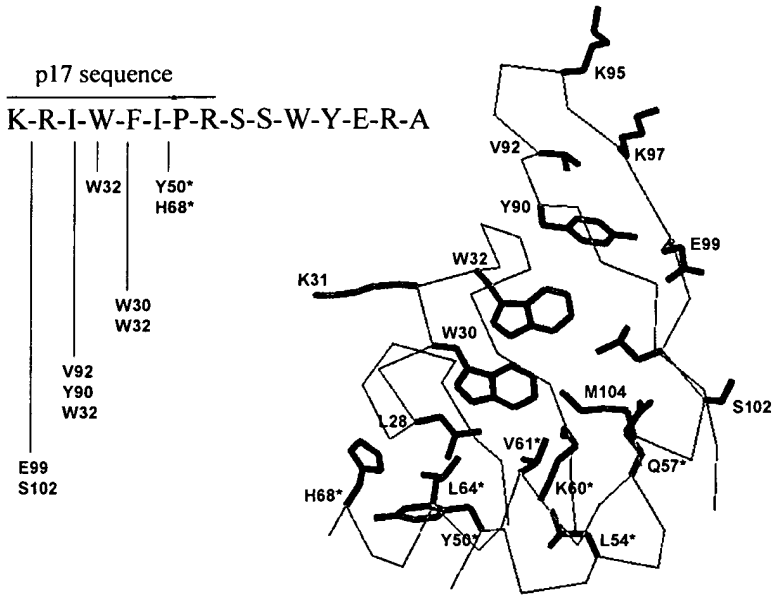


Figure A2.1. *Possible orientation of the amino acid sequence KRIWF from peptide p17 (included within the consensus sequence of "in vivo" active peptides) in the region of the main hydrophobic cavity of TGF-β1.*

The position of the ligand in the main cavity of the TGF-β1 molecule was modelled with the CNS v1.0 software (Brunger A.T. *et al.*, Crystallography & NMR system: A new software suite for macromolecular structure determination: Acta Crystallogr D Biol Crystallogr. 1998 Sep 1;54(Pt 5):905-21.) by a rigid body refinement, followed by a standard protocol of minimization by conjugated gradient and slow cooling. System starting temperature was 3,000°K. During the modelling process, thermal parameter B of each atom from the protein and peptide was maintained at a constant value of 20 A3.

A



B

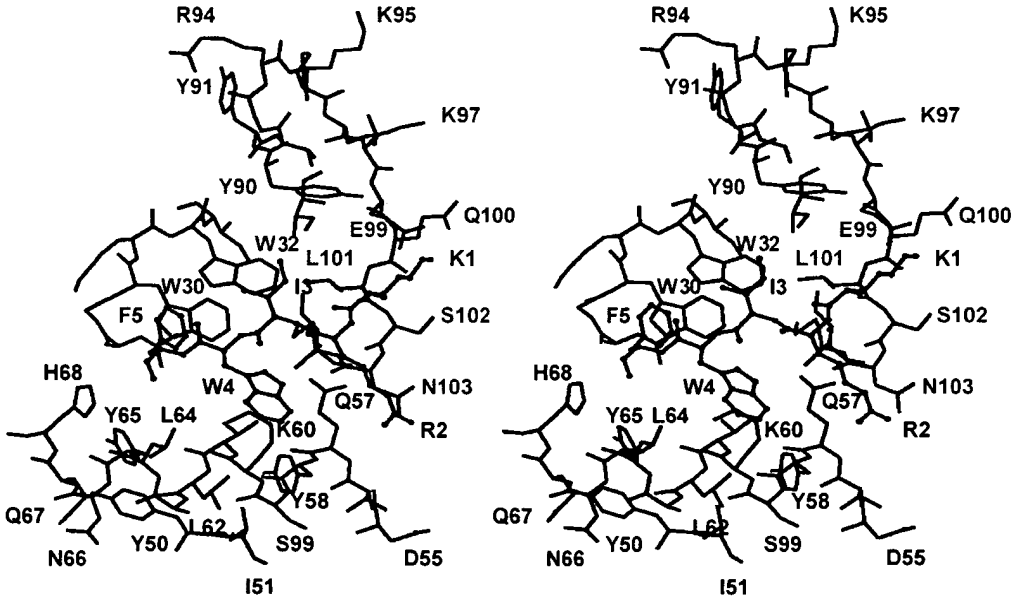


Figure A2.2. *(A) Diagram of the possible interaction between the amino acid sequence KRIWF of peptide p17 and residues located in the main cavity of TGF-β1.* ***(B)*** *Stereo pair illustrating the same interaction as in (A). The amino acids typed in blue and in green differ the residues corresponding to the two monomers which form the active homodimer of TGF-β1, whereas the amino acids typed in red correspond to the p17 fragment.*